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Twenty-Year Outcome Analysis of Genetic Screening Programs for Tay-Sachs and β-Thalassemia Disease Carriers in High Schools

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Summary

Programs for education, screening, and counseling of senior-high-school students, in populations at high risk for Tay-Sachs and β-thalassemia diseases, have existed for >20 years in Montreal. Four process and outcome variables are reported here: (i) voluntary participation rates in the high-school cohort; (ii) uptake rates for the screening test; (iii) origin of carrier couples seeking the prenatal diagnosis option in the programs; and (iv) change in incidence of the two diseases. Between 1972 and 1992, we screened 14,844 Ashkenazi-Jewish students, identified 521 HexA-deficient carriers (frequency 1:28), reached 89% of the demographic cohort in the educational component of the program, and achieved 67% voluntary participation in the subsequent screening phase. The corresponding data for the β-thalassemia program are 25,274 students (mainly of Mediterranean origin) representing 67% of the cohort with 61% voluntary participation in the screening phase (693 carriers; frequency 1:36). From demographic data, we deduce that virtually all the carriers identified in the high-school screening program remembered their status, had their partner tested if they did not already know they were a carrier couple, and took up the options for reproductive counseling/prenatal diagnosis. In Montreal, the current origin of all couples using prenatal diagnosis for Tay-Sachs and β-thalassemia diseases is the corresponding genetic screening/testing program, whereas, at the beginning of the programs, it was always because there was a history of an affected person in the family. Incidence of the two diseases has fallen by 90%–95% over 20 years; the rare new cases are born (with two exceptions) outside the target communities or to nonscreened couples.

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Introduction

β-thalassemia major and Tay-Sachs disease are lethal autosomal recessive phenotypes. The overall carrier frequency for Tay-Sachs alleles is given as 1 in 27 among Ashkenazi Jews (Gravel et al. 1995) and is even higher for β-thalassemia alleles in malarial regions (present or former) of the world (Weatherall et al. 1995). Treatment of β-thalassemia by transfusion and iron chelation reduces and delays severe manifestations of the disease; treatment of Tay-Sachs disease remains palliative. Wherever the burden of these two diseases is perceived to be great by the affected families and communities, avoidance by carrier detection through population screening and genetic testing, coupled with genetic counseling and fetal diagnosis, has become an effective and widespread practice (Kaback et al. 1993; Cao 1994).

Here, we report further details about two screening programs operating in Montreal for >2 decades in communities at high risk for Tay-Sachs disease and β-thalassemia; the participants are senior-high-school students (Beck et al. 1974; Clow and Scriver 1977; Scriver et al. 1984; Zeesman et al. 1984; Ostrowsky et al. 1985). Both programs were introduced shortly after prenatal diagnosis became feasible for the two diseases. The goals, then and now, are (i) to communicate relevant information to the communities at high risk in Quebec; (ii) to identify carriers by reliable screening tests; (iii) to inform the carriers confidentially about their test results; and (iv) to facilitate making informed decisions about reproductive options later in life and to obtain prenatal diagnosis, if desired. Participation is voluntary, and the programs operate with open and continuing sanction of the communities directly concerned with their operation and maintenance. They are examples of "community genetics" (Modell and Kuliev 1991). Our findings indicate a high rate of voluntary participation in high schools, a strong uptake of reproductive counseling options later in life, and a major decline in the incidence of the two diseases in Quebec society.

Methods

The Screening Programs: Structure and Process

We evaluated participation during the years 1973 through 1992, in the Tay-Sachs program, and from

1980 through 1992 in the β-thalassemia program. Both programs are directed at high-school students ≥16 years of age (Scriver et al. 1984; Zeesman et al. 1984); both have been reviewed and approved by the relevant school boards, administrators, screening communities, principals, teachers, and parent-teacher committees.

The programs comprise (i) education; (ii) voluntary participation in the screening (testing) phase; (iii) analysis of the sample in a centralized laboratory with quality control; (iv) reporting of the test results to the participant alone in a confidential manner; and (v) reproductive counseling when requested.

Information sessions are conducted in the schools where the programs operate. All students are included in the invitation to the education session, which covers an introduction to genetic principles, an overview to improve awareness of some prevalent recessive genetic diseases that cluster nonrandomly in human populations (Tay-Sachs, β-thalassemia, sickle cell, and cystic fibrosis diseases are used to illustrate), and an objective description of the disease (Tay-Sachs or β-thalassemia) that is the focus of the program. The rationales for genetic screening (or testing) are explained (National Academy of Science 1975).

In the week following the educational component, the student decides whether to proceed to the screening component. Participation at this level is voluntary but requires a form signed by the participant and a parent. A blood sample is then taken from the consenting individual. The test result is reported directly and only to the participant, in a self-addressed envelope. Each test result is accompanied by a signed letter of interpretation. Carriers are contacted later by telephone to offer further interpretation and counseling.

Analytical

Tay-Sachs program.—Analysis of serum hexosaminidase activity (Hex A and Hex B isoenzymes) is performed by a semiautomated, heat-denaturation assay with 4-methylumbelliferyl N-acetyl glucosaminide (4MUG) substrate (Delvin et al. 1972). Results are classified as carrier or noncarrier by a Bayesian density discriminant function (Gold et al. 1974). Ambiguous results are resolved by an assay using the sulfated substrate (Bayleran et al. 1984) or by mutation analysis (Fernandes et al. 1992).

β-thalassemia program.—The erythrocyte phenotype is measured in an EDTA-treated blood sample in two stages (Scriver et al. 1984); by mean red cell volume in a Coulter counter; by HbA_2 analysis of samples with an mean red cell volume (MCV) value <76 fl. Results are classified by a Bayesian density discriminant function (Zannis-Hadjopoulos et al. 1977). Additional tests are performed when indicated.

Census data.—The communities served by the screening programs are located in the Montreal region, which contains half the Quebec population. Community size was estimated from local information and Canadian census data. In the Ashkenazi-Jewish community, 1,241 persons in the annual cohort of 16 year olds could claim Jewish ancestry for one or both parents; the corresponding number of carriers (for Tay-Sachs disease) would be 44 per year. In the β-thalassemia (Mediterranean) community, the corresponding cohort was 4,736 students and an estimated 132 carriers.

Demographic factors.—We compared the theoretical (full) participation rate with the observed (actual) rates for a 20-year period in the Tay-Sachs screening program (1973–1992, inclusive) and for a 13-year period in the β-thalassemia program (1980–1992). We made the following assumptions (Drummond 1980; Statistics Canada 1980): (i) Couples in Quebec begin their reproductive years at age 23, on average; accordingly, only individuals in the first 13 years of the Tay-Sachs screening program and the first 6 years of the β-thalassemia program were included to calculate the expected frequencies of affected fetuses. (ii) Couples of self-declared Italian, Greek, or Jewish affiliation in Montreal have two children, on average, during their reproductive lives; accordingly, there would be two diagnostic procedures per carrier couple. And (iii) the endogamy rates in the Greek and Italian communities and in the Ashkenazi-Jewish community were each 75%.

Pregnancy outcome review.—Prenatal diagnosis for Tay-Sachs disease and β-thalassemia is done at one regional center in the province. We reviewed the charts for all consultands receiving prenatal counseling for these two diseases and recorded context of the referral (affected family member or carrier status identified by screening only), pregnancy history, number of fetal diagnoses performed, test result, and outcome of pregnancy.

Results

The Tay-Sachs Program

Efficiency of the screening component.—In the designated 20-year interval, we screened 14,844 students and detected 521 carriers (carrier rate 1 in 28). We reached 89% of the demographic cohort in the educational session, of whom 67% were screened.

How TSD carriers use the test result.—We estimated that the high-school cohort harbored 16 couples (rounded from 15.4) who would have their children within the time frame of our analysis. Ten carrier couples identified by screening sought prenatal diagnosis, the predicted number in the screened cohort. They had 15 pregnancies, all monitored for an affected fetus. Three affected pregnancies were terminated voluntarily; 12 unaffected offspring were born.

Origins of TSD carrier couples.—Prenatal diagnosis

Table 1

Source of Referrals and Outcomes of Prenatal Diagnosis Component of Tay-Sachs Screening Program in Quebec (Ashkenazi-Jewish Community)

	Reason for Referral of Couple		
	Affected Offspring	Screening Program	Total
No. of couples	6	10	16
No. of pregnancies monitored	15	17	32
No. of affected fetuses	4	4	8
No. of elective terminations	4	4	8
No. of unaffected liveborns	11	13	24

for Tay-Sachs disease became available in Quebec in 1973; 16 couples have sought prenatal diagnosis during this time. Initially the basis for referral was an affected child in the family (6 couples); all referrals for prenatal counseling and diagnosis now originate from screening (10 couples) (table 1 and fig. 1). The "screened carrier couples" were of two types: both partners identified by high-school screening or one partner so identified and the unscreened partner then tested.

Incidence of Tay-Sachs disease in Quebec.—Only one affected infant has been born in the Ashkenazi-Jewish community since inception of the carrier screening program; the parents were a nonscreened couple. Three other cases of Tay-Sachs disease have occurred in the province all from a regional non-Jewish deme outside the Montreal program, where the disease originates in a novel "non-Jewish" deletion mutation with founder effect (DeBraekeleer et al. 1992). In each case, the carrier couple had not been tested. Families in the deme have since taken up cascade carrier testing and reproductive counseling. The overall incidence of Tay-Sachs disease in the province has fallen by 90% in 20 years, reflecting both a general decline in birthrate in Quebec and the effect of carrier screening in the two populations.

The β-Thalassemia Program

Efficiency of the screening component.—We screened 25,274 students and detected 693 carriers (carrier rate 1 in 36). We reached 67% of the demographic cohort in the educational sessions, of whom 61% were screened.

How β-thalassemia carriers use the information.—We estimated that the high-school cohort harbored 16 carrier couples who would have children in the time frame of our analysis. There were nine carrier couples identified by screening who sought prenatal diagnosis, the predicted number in the screened cohort. They had 14 pregnancies, all monitored by prenatal diagnosis. One couple requested to have counseling only and elected to have no children. Fetal diagnosis detected three affected pregnancies; each was terminated, by choice. A single known false-negative fetal diagnosis, due to maternal contamination of a CVS sample and a PCR amplification error, resulted in one affected liveborn infant. Ten unaffected offspring were born to the screened carrier couples.

Origins of β-thalassemia carrier couples.—Prenatal diagnosis for β-thalassemia became available in Quebec in the mid-1970s; 32 couples have sought prenatal diagnosis since then, 24 originating from the screening program (table 2). A positive family history for an affected member was the initial reason why couples sought to avoid recurrence of the disease. Now, identification of carrier couples, either by the screening program or by genetic testing within the community, is the universal reason for referral (fig. 2). As was the case in the Tay-Sachs disease program, there were two types of screened carrier couples: one where both partners were detected by high-school screening; in the other, one partner was so identified and the other then tested and detected.

Prenatal counseling and diagnosis in the global program has led to the birth of 43 unaffected children and 11 voluntary terminations of an affected fetus. There has been one misdiagnosis (table 2).

Incidence of β-thalassemia in Quebec.—Two children with β-thalassemia major have been born since inception of the program. One was the result of a false-negative β-thalassemia fetal diagnosis (maternal contamination of CVS); the other was born to a nonscreened couple. Incidence of the disease has fallen by 95% in the 13 years of the program, reflecting both a general decline in birthrate and a specific effect of the program.

Discussion

This study evaluates three factors not previously measured in the screening programs to detect carriers of

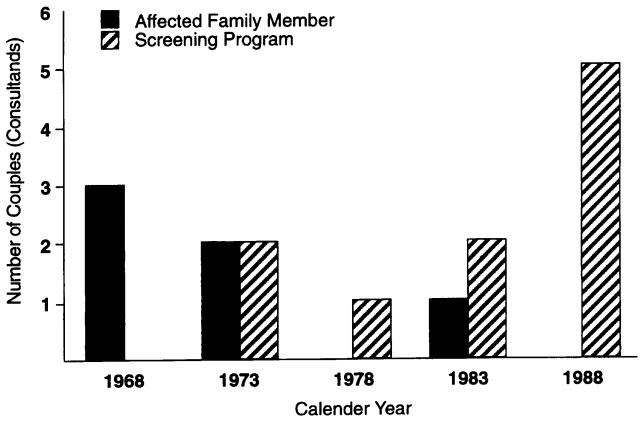

Figure 1 Numbers and origins of referrals for prenatal diagnosis, by year, in the Montreal-based genetic screening program for prevention/avoidance of Tay-Sachs disease.

Table 2

Source of Referrals and Outcomes of Prenatal Diagnosis Component of the β-Thalassemia Screening Program in Quebec ("Mediterranean" Community)

	Reason for Referral of Couple		
	Affected Offspring	Screening/ Testing[a]	Total
No. of couples	8	24	32
No. of pregnancies monitored	16	40	56
No. of affected fetuses	4	8 + (1)[b]	13
No. of elective terminations	3	8	11
No. of affected liveborns	1	1[b]	2
No. of unaffected liveborns	12	31	43

[a] An additional 10 couples came forward outside of the high school screening projects because of the community effort to add genetic testing along with screening.

[b] This fetus was affected but not diagnosed until after birth. The false-negative fetal diagnosis was attributed to maternal contamination of the chorionic villus sample.

Tay-Sachs and β-thalassemia alleles in Montreal. Here we report (i) participation rates in the educational, screening, and prenatal diagnosis components of the programs; (ii) the changing source of referrals for prenatal diagnosis over time in the programs; and (iii) the decline in incidence rates of the corresponding diseases.

Participation Rates

Genetic screening addresses populations; genetic testing is used by individuals and families at particular risk (Congress of the United States, Office of Technology Assessment 1992; Andrews et al. 1994). The Montreal programs for avoidance of Tay-Sachs and β-thalassemia diseases have employed screening rather than testing, up to now. However, as the educational components of the programs permeate the Montreal communities, genetic testing is on the increase in what could be called a "community genetics" initiative (Modell and Kuliev 1991). Genetic testing by analysis of whole blood is feasible for β-thalassemia, because the tests (MCV and HbA_2 measures) are conventional in many hematological and local laboratories; on the other hand, testing for Tay-Sachs disease heterozygosity by enzyme assay requires specialized handling of the serum sample and measurement of serum hexosaminidase activity and statistical handling of the test result. Accordingly, testing may replace screening in Montreal as the major process in β-thalassemia disease prevention in Montreal, but is less likely to do so for Tay-Sachs disease.

The present report is the latest in a series of outcome evaluations in high-school programs for genetic screening and testing of carriers harboring prevalent recessive alleles (e.g., Tay-Sachs disease, β-thalassemia, and cystic fibrosis) (Beck et al. 1974; Clow and Scriver 1977; Scriver et al. 1978, 1984; Zeesman et al. 1984; Mitchell et al. 1993). We have now measured participation rates in the cohort of senior-high-school age (16 years and over); note that, in Quebec, persons ≥14 years of age can seek health care on their own recognizance. Whether participation in the screening component of our high-school programs is truly voluntary or reflects peer pressure and group dynamics is moot, but two incidents are informative here: a pair of screening sessions at two different schools were scheduled accidentally on pedagogical holidays when classes did not take place; nonetheless, students confirmed that testing would be available and returned to be tested at 65% and 85% participation rates—on the holidays.

The screening rate was 67% in the Tay-Sachs program, and we estimate that we detected 59% of the carriers in the total community cohort. In the β-thalassemia program, the screening rate was 61%, and we estimate that we detected 41% of the carriers in the community cohort. However, because of demographic trends and other factors in the Mediterranean communities, students are now more likely to attend schools not currently affiliated with our screening program than was the case at the outset. Accordingly, the ongoing programs will evolve and put in place alternative resources for testing as well as screening.

Referral Source for Prenatal Diagnosis

We next evaluated how the information gained in the screening program was used by carriers later in their lives. The rate of uptake in the prenatal diagnostic phase is very high (approaching 100%) among carrier couples where one or both partners were initially identified by screening in high-school programs. During the time the

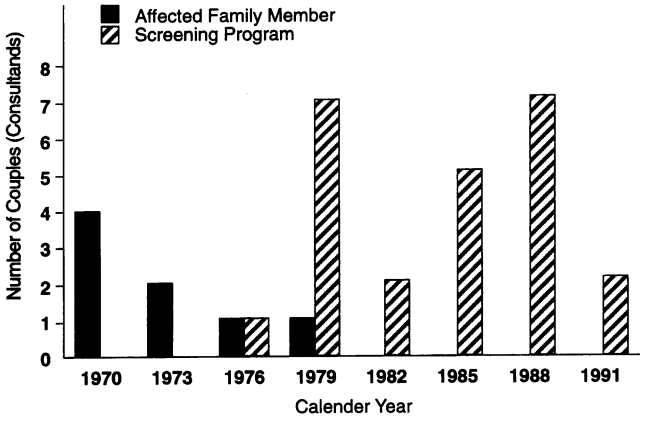

Figure 2 Numbers and origins of referrals for prenatal diagnosis by year, in the Montreal-based genetic screening program for prevention/avoidance of β-thalassemia major.

programs have been operating, there has been a significant transition in the rationale for seeking prenatal diagnosis. Initially it was because of an affected case in the family. With no exception, those who now seek prenatal diagnosis discovered their status in the screening programs.

There are concerns (Andrews et al. 1994; Scriver 1995) about genetic screening in high schools. However, an earlier study in Montreal showed that high-school students in Montreal have a high level of interest in genetics (Scriver et al. 1978). As implied by the present findings, "carrier students" remember their status, are not stigmatized by it, and use the genetic information in ways they deem helpful. A repertoire of anecdotes supports these viewpoints and the broad acceptance of community genetics; the data buttress them.

The relevance of prenatal diagnosis for families at risk for Tay-Sachs and β-thalassemia diseases is as apparent in Quebec as it is elsewhere (Kaback 1993; Cao 1994); couples at risk conceive and have healthy children; this was the primary goal of the programs. In the meantime, mutation analysis and data on relative frequencies for *HEXA* alleles (Fernandes et al. 1992) and *HBB* β-thalassemia alleles (Kaplan et al. 1991) in the relevant communities have facilitated prenatal diagnosis. Although there are no formal statistics from the Montreal communities, it is understood that, without access to prenatal diagnosis, couples at risk for Tay-Sachs disease and β-thalassemia would be less fertile. Since the prenatal diagnosis option permitted families to have children, it has had the same positive influence on fertility in Quebec families as noted elsewhere (Modell et al. 1980; Kaback et al. 1993; Cao 1994).

Could the high rate of uptake for prenatal diagnosis have been achieved otherwise? The answer is yes, if genetic testing (vs. screening) were universally accessible and utilized. Earlier, this was shown not be to an efficient option in Montreal (Beck et al. 1974; Scriver et al. 1984), and we turned to the screening approach. Otherwise, it is unlikely that the efficacy of the prenatal diagnosis component of the program, and its effect on incidence of the target diseases, would be as great as we describe here.

Effect on Incidence

The Quebec health care system lists diagnoses of diseases and frequency. Incidence rates for Tay-Sachs disease and β-thalassemia livebirths have both declined in Quebec province since our programs began, and we know that 19 affected cases were not born over the past 2 decades. We know also that the rare new cases have particular explanations. However, the marked decrease in incidence cannot be attributed solely to the screening programs; the decline in birth rate accounts for about half the effect.

Economic analyses of the two programs (Dagenais et al. 1985; Ostrowsky et al. 1985) showed they were either cost-neutral or cost-effective. The per-person costs for the carrier screening tests (in 1994 Canadian dollars) are $36.32 for Tay-Sachs disease (HexA assay with 4-MUG) and $16.33 for β-thalassemia (for MCV and, when indicated, HbA_2). Since economy of scale is important in times of change in health care policy and infrastructure and as costs rise (Arrow et al. 1985; Evans 1988), there is an economic reason to maintain the two programs.

Genetics in health care must be ethical and used in ways that honor the principles of autonomy, justice, privacy, equity, and quality (Knoppers and Chadwick 1994). In our case, the programs have also taken into account ethical, legal, and psychosocial implications for adolescents (ASHG/ACMG 1995). The Montreal programs honor autonomy of the communities, families, and individuals and accommodate issues special to the adolescent group; because of our health care system (Evans 1988), justice and equity are being served; privacy is honored in the way test results are distributed only to participating consultands; and quality is maintained by formal monitoring of laboratory performance in the international project (Kaback et al. 1993) and by the ongoing evaluation of process and outcome, of which this report is an example.

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